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GARS1-Associated Axonal Neuropathy

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Summary

Clinical characteristics

The phenotypic spectrum of *GARS1*-associated axonal neuropathy ranges from *GARS1* infantile-onset SMA (*GARS1*-iSMA) to *GARS1* adolescent- or early adult-onset hereditary motor/sensory neuropathy (*GARS1*-HMSN).

- ***GARS1*-iSMA**. Age of onset ranges from the neonatal period to the toddler years. Initial manifestations are typically respiratory distress, poor feeding, and muscle weakness (distal greater than proximal). Weakness is slowly progressive, ultimately requiring mechanical ventilation and feeding via gastrostomy tube.
- ***GARS1*-HMSN**. Age of onset is most commonly during the second decade (range eight to 36 years). Initial manifestations are typically muscle weakness in the hands sometimes with sensory deficits. Lower limb involvement (seen in ~50% of individuals) ranges from weakness and atrophy of the extensor digitorum brevis and weakness of toe dorsiflexors to classic peroneal muscular atrophy with foot drop and a high steppage gait.

Diagnosis/testing

The diagnosis of *GARS1*-associated axonal neuropathy is established in a proband with suggestive clinical findings and a heterozygous pathogenic variant in *GARS1* identified by molecular genetic testing.

Management

Treatment of manifestations:

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- ***GARS1*-iSMA**. Supportive treatment should be tailored to the needs of the affected individual and his/her current functional status (non-sitter, sitter, or walker). A multidisciplinary team to include a neurologist, pulmonologist, physiatrist, and medical geneticist is recommended.
- ***GARS1*-HMSN.** Symptomatic treatment includes facilitating activities of daily living and addressing of mobility needs by a multidisciplinary team that includes neurologists, physiatrists, orthopedic surgeons, and physical and occupational therapists.

Surveillance:

- ***GARS1*-iSMA.** Routine monitoring of: growth, nutritional status, safety of oral feeding vs gastric tube feeding, respiratory status, need for assistive devices for activities of daily living and mobility, developmental progress and educational needs, and family need for social work support.
- ***GARS1*-HMSN.** Routine monitoring of neurologic findings, physical therapy and occupational therapy needs, and skin for pressure ulcers or sores and skin breakdown (particularly the feet, hips, and other pressure points).

Agents/circumstances to avoid: Medications that are toxic or potentially toxic to persons with HMSN.

Evaluation of relatives at risk: It is appropriate to clarify the genetic status of apparently asymptomatic older and younger at-risk relatives of an individual with ***GARS1*-HMSN** in order to identify as early as possible those who would benefit from prompt initiation of symptomatic management and awareness of agents/circumstances to avoid.

Genetic counseling

GARS1-associated axonal neuropathy is an autosomal dominant disorder.

- ***GARS1*-iSMA.** All probands reported to date with the *GARS1*-iSMA phenotype whose parents have undergone molecular genetic testing have the disorder as a result of a *de novo GARS1* pathogenic variant. If the *GARS1* pathogenic variant cannot be detected in the leukocyte DNA of either parent, the recurrence risk to sibs is estimated to be 1% because of the theoretic possibility of parental germline mosaicism.
- ***GARS1*-HMSN.** Most individuals diagnosed with the *GARS1*-HMSN phenotype have an affected parent. Each child of an individual with *GARS1*-HMSN is at a 50% risk of inheriting the *GARS1* pathogenic variant.

Once the *GARS1* pathogenic variant has been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing are possible.

GeneReview Scope

GARS1-Associated Axonal Neuropathy: Included Phenotypes [1]
• *GARS1* infantile-onset spinal muscular atrophy (*GARS1*-iSMA) • *GARS1* adolescent- or early adult-onset hereditary motor/sensory neuropathy (*GARS1*-HMSN) [2]

For synonyms and outdated names see Nomenclature.
1. For other genetic causes of these phenotypes see Differential Diagnosis.
2. GARS1-HMSN encompasses the phenotypes also referred to as Charcot-Marie-Tooth neuropathy type 2D (CMT2D) and distal spinal muscular atrophy V (dSMA-V).

Diagnosis

No consensus clinical diagnostic criteria for *GARS1*-associated axonal neuropathy have been published.

Suggestive Findings

GARS1-associated axonal neuropathy **should be suspected** in individuals with the following clinical findings; findings on EMG and neuroimaging; and family history.

Clinical Findings

***GARS1* infantile-onset spinal muscular atrophy (*GARS1*-iSMA)**

- Typically, infantile onset of respiratory distress, poor feeding, and muscle weakness, with distal weakness greater than proximal; however, some children may present with features similar to toddlers.
- Absence of molecular genetic findings of spinal muscular atrophy (SMA) (i.e., either biallelic *SMN1* deletions or compound heterozygosity for an *SMN1* deletion and an *SMN1* sequence variant)

***GARS1* adolescent- or early adult-onset hereditary motor/sensory neuropathy (*GARS1*- HMSN)**

- Bilateral weakness and atrophy of thenar and first dorsal interosseous muscles with progression to involve hypothenar, foot, and peroneal muscles in many individuals and mild-to-moderate impairment of vibration sense developing in advanced illness in some individuals (see Figure 1)
- Sensory deficits including reduction of pinprick, temperature, touch, and vibration perception in a stocking and (less often) glove pattern

Electrophysiologic Studies

EMG shows denervation predominantly in the distal muscle groups at normal motor distal latencies and conduction velocities (see Table 1; pdf):

- Absent or markedly reduced (frequently <1 mV) compound muscle action potentials (CMAPs) are recorded from the abductor pollicis brevis (APB) by median nerve stimulation [Sivakumar et al 2005].
- Preserved CMAPs are recorded from the abductor digiti minimi (ADM) by ulnar nerve stimulation.
- CMAP amplitude recorded by stimulation of the peroneal nerve is <2 mV in most individuals and <1 mV in individuals having clinically evident leg atrophy.
- Normal median SNAP amplitudes and conduction velocities are seen in most individuals, even those with mildly prolonged distal motor latency.
- In individuals with advanced disease, needle EMG shows no voluntary motor activity in the abductor pollicis and first dorsal interossei because of marked atrophy. Spontaneous activity is often seen in these muscles.
- The elicited sural SNAPs are preserved but with a reduced amplitude, despite sensory axonal loss identified histopathologically on examination of a sensory nerve from an individual with the CMT2D subtype; similar but milder changes were seen in individuals with dSMA-V.

Note: EMG is more widely available than nerve biopsy, which can be used in a single individual in a family or in diagnostically difficult cases.

Neuroimaging. Magnetic resonance imaging of the spine may demonstrate volume loss of ventral nerve roots, best appreciated at the cauda equina. Brain MRI is normal [Markovitz et al 2020].

Family history. The affected individual represents a simplex case (i.e., a single occurrence in a family) or has a family history consistent with autosomal dominant inheritance (e.g., affected males and females in multiple generations).

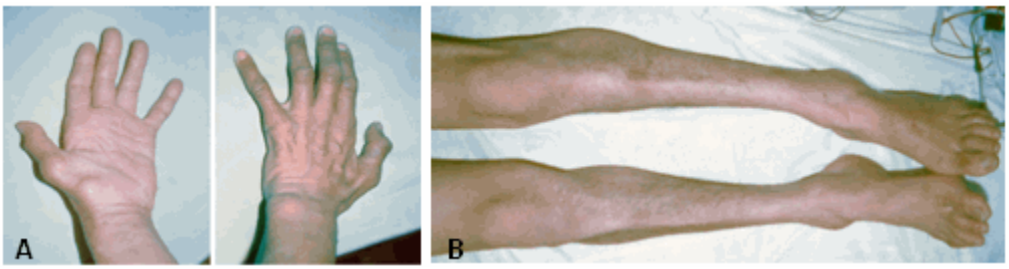

Figure 1. Distribution of muscle weakness and atrophy in individuals with two major clinical phenotypes of *GARS1*-associated disease

A. Thenar and first dorsal interosseus muscle wasting with relatively preserved hypothenar in an individual with dSMA-V phenotype

B. Peroneal atrophy, *pes cavus*, and hammerhead toes in an individual with the CMT2D phenotype; this individual also has a reduction of pinprick, temperature, touch, and vibration sense in stocking distribution.

Reprinted from Sivakumar et al [2005] by permission of Oxford University Press

Establishing the Diagnosis

The diagnosis of *GARS1*-associated axonal neuropathy **is established** in a proband with suggestive clinical findings and a heterozygous pathogenic variant in *GARS1* identified by molecular genetic testing (see Table 2).

Note: Identification of a heterozygous *GARS1* variant of uncertain significance does not itself establish or rule out the diagnosis of this disorder.

The molecular genetic testing approach will likely depend on the age of onset of disease manifestations.

For an infant or a toddler, initial testing is typically *SMN1* molecular genetic testing for spinal muscular atrophy, followed by either a multigene panel or comprehensive genomic testing, which does not require the clinician to determine which gene is likely involved. Exome sequencing is most commonly used; genome sequencing is also possible.

For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

Note that commercial multigene panels for early-onset neuropathies may often not include *GARS1*.

For individuals presenting in adolescence or adulthood, a hereditary motor and sensory neuropathy (also called Charcot-Marie-Tooth [CMT] hereditary neuropathy or distal hereditary neuropathy) multigene panel that includes *GARS1* and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

Table 2. Molecular Genetic Testing Used in *GARS1*-Associated Axonal Neuropathy

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant [2] Detectable by Method
GARS1	Sequence analysis [3]	100% [4]
	Gene-targeted deletion/duplication analysis [5]	None reported

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on allelic variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Data derived from the subscription-based professional view of Human Gene Mutation Database [Stenson et al 2017]
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.

Clinical Characteristics

Clinical Description

Individuals with *GARS1*-associated axonal neuropathy can present across the life span (infancy through adulthood). Although in utero presentation of a fetus with a *GARS* pathogenic variant has not been reported to date, it is possible (if not likely) given reports of in utero presentations of spinal muscular atrophy [MacLeod et al 1999, Kong et al 2021]. *GARS1* infantile-onset SMA presents with respiratory distress, poor feeding, and muscle weakness that is distal greater than proximal. *GARS1* adolescent- or early adult-onset hereditary motor/sensory neuropathy presents from childhood to adulthood, most commonly with muscle weakness in the hands and sometimes with sensory deficits in a stocking and (less often) glove pattern.

GARS1 Infantile-Onset Spinal Muscular Atrophy (*GARS1*-iSMA)

Age of onset ranges from the neonatal period to the toddler years. The presenting manifestations are typically respiratory distress, poor feeding, and muscle weakness (distal weakness greater than proximal).

Neonates present emergently with respiratory distress (stridor, weak cry, and respiratory insufficiency), poor feeding, and severe hypotonia, ultimately requiring mechanical ventilation and early placement of a gastrostomy tube. In neonates, the neurologic examination is notable for hypotonia, hyporeflexia, and tongue fasciculations in some.

Infants typically have delayed motor milestones with subsequent motor milestone regression. They do not achieve independent walking [James et al 2006, Eskuri et al 2012, Liao et al 2015]. Toddlers present with delayed walking and lack of stability progressing to loss of ambulation [Liao et al 2015]. Infant and toddler examinations are notable for hypotonia, absent or diminished reflexes, and stridor in some.

Nerve/muscle biopsy. Hematoxylin and eosin stain of quadriceps muscle of an infant show marked variation in fiber size with small group and fascicular atrophy typical of spinal muscular atrophy (see Figure 2).

GARS1 Adolescent- or Early Adult-Onset Hereditary Motor/Sensory Neuropathy (*GARS1*-HMSN)

Age of onset ranges from eight to 36 years, with most individuals (75%) developing manifestations during the second decade of life [Sivakumar et al 2005, James et al 2006].

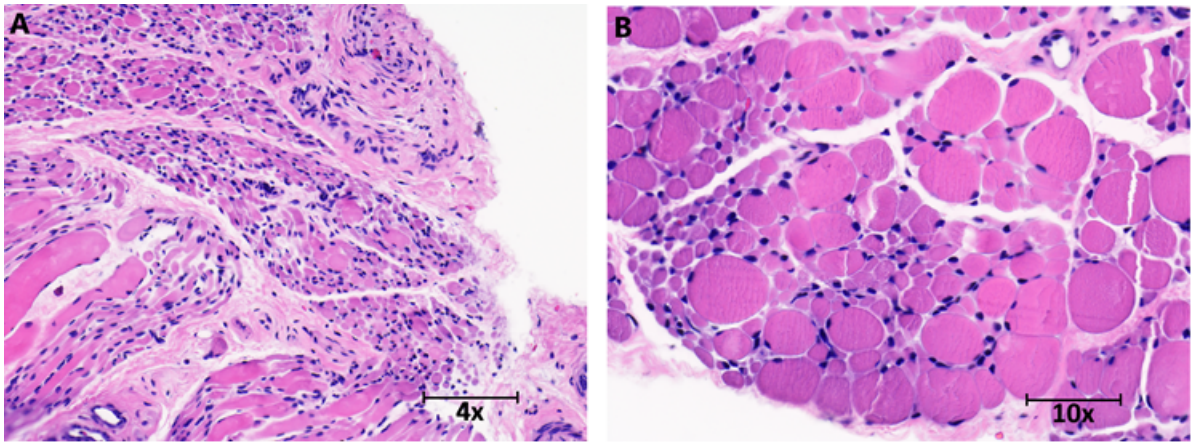

Figure 2. Hematoxylin and eosin stain of quadriceps muscle of an infant with *GARS1*-iSMA at 4X (A) and 10X (B) magnification showing findings typical of spinal muscular atrophy

A. Low power magnification demonstrates small atrophied fibers with marked variation in fiber size. Inflammatory cells are absent, and there is no increase in endomysial connective tissue.

B. Higher power magnification demonstrates clusters of large hypertrophied muscle fibers among large groups of small often rounded, atrophic muscle fibers.

The presenting manifestation is typically muscle weakness, often initially evident as transient cramping and pain in the hands on exposure to cold and cramping in calf muscles on exertion. Progressive weakness and atrophy of the thenar and first dorsal interosseus muscles are the major complaints (Figure 1). The hypothenar eminence is spared until later in the disease course.

The lower limbs are involved in about 50% of affected individuals. Lower-extremity involvement ranges from weakness and atrophy of the extensor digitorum brevis and weakness of toe dorsiflexors to classic peroneal muscular atrophy with foot drop and a high steppage gait. Peroneal muscles are affected earlier and more severely than the calf muscles. Peroneal muscular atrophy is associated with *pes cavus* and moderate sensory abnormalities. Reflexes at the ankles are diminished or absent in individuals with leg muscle weakness and sensory deficits.

Proximal limb muscle weakness is not observed in the upper or lower extremities.

Sensory examination is either normal or shows mild-to-moderate impairment of vibration sense in the hands and feet and reduction of pinprick, temperature, touch, and vibration perception in a stocking and (less often) glove pattern.

A minority of individuals show upper motor neuron signs (mild pyramidal signs and spasticity) [Christodoulou et al 1995, Sivakumar et al 2005, Dubourg et al 2006]. The occurrence of upper motor neuron signs may be attributed to relative preservation of sensory nerves and involvement of central motor pathways.

While progression of manifestations is often slow, extending over decades, some individuals may have a more rapid evolution of lower extremity involvement, which may more often be seen in the setting of both motor and sensory changes [Dubourg et al 2006].

Genotype-Phenotype Correlations

***GARS1*-iSMA.** *GARS1* pathogenic variants in the catalytic or anticodon binding domain are associated with this phenotype: p.Gly652Arg, p.Ile334Asn, p.Gly652Ala, and p.Asp200Tyr.

***GARS1* adolescent- or early adult-onset HMSN**

- *GARS1* variants associated exclusively with distal spinal muscular atrophy V (dSMA-V): p.Leu183Pro and p.His472Arg.
- *GARS1* variants associated with Charcot-Marie-Tooth neuropathy type 2D (CMT2D): p.Gly294Arg, p.Ile334Phe, and p.Gly580Arg.
- *GARS1* variants associated with both dSMA-V and CMT2D: p.Glu125Gly, p.Pro298Leu, and p.Asp554Asn

Penetrance

To the authors' knowledge, reduced penetrance has not been described for *GARS1*-iSMA.

For adolescent- or adult-onset *GARS1*-HMSN, variable expressivity is described and at least one example of non-penetrance has been reported [Yalcouyé et al 2019].

Nomenclature

***GARS1* infantile-onset spinal muscular atrophy (*GARS1*-iSMA).** In this *GeneReview, GARS1*-iSMA is used to denote early-onset SMA (from the neonatal period to toddler age, presenting with respiratory insufficiency, poor feeding, hypotonia and areflexia).

***GARS1* adolescent- or early adult-onset hereditary motor/sensory neuropathy (*GARS1*-HMSN)**

- **Charcot-Marie-Tooth neuropathy type 2D (CMT2D)** and **distal spinal muscular atrophy V (dSMA-V)** were originally thought to be distinct entities. However, subsequent family studies [Sambuughin et al 1998] and later molecular genetic studies [Antonellis et al 2003] determined that they represent the clinical spectrum of adolescent- or early adult-onset HMSN caused by pathogenic variants in *GARS1*. CMT2D and dSMA-V are now collectively referred to as *GARS1*-HMSN. (See also CMT Hereditary Neuropathy Overview, Nomenclature.)
- **CMT2D** – characterized by distal motor and sensory neuropathy – may also be referred to as *GARS1*-associated distal motor and sensory neuropathy or, using the classification system proposed by Magy et al [2018], AD-CMTAx-*GARS1*.
- **dSMA-V** – characterized exclusively by distal motor involvement – may also be referred to as *GARS1*-associated distal hereditary motor neuropathy (*GARS1*-dHMN).

Prevalence

Disease prevalence is unknown; *GARS1*-associated axonal neuropathy is likely very rare. For example, fewer than 50 *GARS1* pathogenic variants have been described; the vast majority are not recurrent [Meyer-Schuman & Antonellis 2017, Markovitz et al 2020].

Genetically Related (Allelic) Disorders

Biallelic germline pathogenic variants in *GARS1* are associated with a multisystem phenotype that includes severe prenatal-onset growth restriction and developmental delays [Oprescu et al 2017].

Differential Diagnosis

Infantile-Onset Spinal Muscular Atrophy

Table 3. Hereditary Disorders with Hypotonia in the Differential Diagnosis of *GARS1* Infantile-Onset Spinal Muscular Atrophy (*GARS1*-iSMA)

Gene(s) or Region	DiffDx Disorder	MOI	Additional Features Overlapping w/*GARS1*-iSMA	Features of DiffDx Disorder Not Associated w/*GARS1*-iSMA
15q11.2-q13 [1]	Prader-Willi syndrome	See footnote 1.	Feeding difficulties	Rarely assoc w/poor respiratory effort
CHAT *CHRNE* *COLQ* *DOK7* *GFPT1* *RAPSN* [2]	Congenital myasthenic syndromes	AR AD	Hypotonia	Ophthalmoplegia, ptosis, episodic respiratory failure
COL6A1/2/3*FKRP* FKTN *CRPPA (ISPD)* LAMA2 *LARGE1* *LMNA* *POMGNT1* *POMT1* *POMT2* *SELENON* (many additional genes) [3]	Congenital muscular dystrophy	AR AD	Muscle weakness, respiratory failure, epilepsy	↑ CK, CNS malformation & leukoencephalopathy, eye involvement
DMPK	Congenital myotonic dystrophy type 1	AD	Muscle weakness	Marked facial weakness w/"myopathic" facies
GAA	Infantile-onset Pompe disease	AR	Feeding difficulties, respiratory failure, hypotonia	EKG abnormalities, cardiomegaly
IGHMBP2	AR dSMA 1 [4] (SMARD) (OMIM 604320)	AR	Areflexia, respiratory failure	Diaphragmatic paralysis
PEX family of genes	Zellweger spectrum disorder	AR [5]	Muscle weakness, poor respiratory effort	Hepatomegaly, large anterior fontanelle, CNS involvement
SMN1	Spinal muscular atrophy	AR	Areflexia, respiratory failure, tongue fasciculations	Sensory involvement, predominant distal weakness

Table 3. continued from previous page.

Gene(s) or Region	DiffDx Disorder	MOI	Additional Features Overlapping w/*GARS1*-iSMA	Features of DiffDx Disorder Not Associated w/*GARS1*-iSMA
UBA1	X-linked infantile SMA	XL	Weakness, areflexia, tongue fasciculations	Multiple congenital contractures, intrauterine fractures

AD = autosomal dominant; AR = autosomal recessive; CK = creatine kinase; DiffDx = differential diagnosis; dSMA = distal spinal muscular atrophy; iSMA = infantile spinal muscular atrophy; MOI = mode of inheritance; SMARD = spinal muscular atrophy with respiratory distress; XL = X-linked

1. Prader-Willi syndrome (PWS) is caused by an absence of expression of imprinted genes in the paternally derived PWS / Angelman syndrome region (15q11.2-q13) of chromosome 15 by one of several genetic mechanisms (paternal deletion, maternal uniparental disomy 15, and rarely an imprinting defect). The risk to the sibs of an affected child of having PWS depends on the genetic mechanism that resulted in the absence of expression of the paternally contributed 15q11.2-q13 region.

2. Pathogenic variants in one of multiple genes encoding proteins expressed at the neuromuscular junction are currently known to be associated with subtypes of CMS. The most commonly associated genes include those listed in the table (see Congenital Myasthenic Syndromes).

3. Multiple genes are associated with congenital muscular dystrophy (CMD). The frequency of CMD subtypes vary by population [Bönnemann et al 2014]. Selected examples of some of the more commonly associated genes are listed in the table.

4. SMARD spans a phenotypic spectrum [Guenther et al 2007].

5. Zellweger spectrum disorder (ZSD) is typically inherited in an autosomal recessive manner (one *PEX6* variant, p.Arg860Trp, has been associated with ZSD in the heterozygous state).

Other inherited disorders to consider in the differential diagnosis of *GARS1*-iSMA include congenital myopathies (see X-Linked Centronuclear Myopathy) and metabolic/mitochondrial myopathies (see Glycogen Storage Diseases [GSD I, GSD II, GSD III, GSD IV, GSD V, GSD VI] and Mitochondrial Disorders Overview).

Infantile botulism may also resemble *GARS1*-iSMA. Like *GARS1*-iSMA, botulism in infants is associated with hyporeflexia, hypotonia, and muscle weakness. Unlike *GARS1*-iSMA, botulism is also associated with proximal weakness.

Adolescent- or Early Adult-Onset Hereditary Motor/Sensory Neuropathy (Charcot-Marie-Tooth Hereditary Neuropathy)

GARS1 adolescent- or early adult-onset hereditary motor/sensory neuropathy (HMSN) needs to be distinguished from other forms of HMSNs characterized by distal muscular atrophy, loss of reflexes, sensory deficits, reduced sensory nerve action potentials (SNAPs), and normal or mildly slowed motor nerve conduction velocity. The unique pattern of hand involvement before leg involvement and preserved SNAPs helps distinguish *GARS1* adolescent- or early adult-onset HMSN from other axonal HMSNs. (See Charcot-Marie-Tooth Hereditary Neuropathy Overview).

Management

No clinical practice guidelines for *GARS1*-associated axonal neuropathy have been published.

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with *GARS1*-associated axonal neuropathy, the evaluations summarized in Tables 4 and 5 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 4. Recommended Evaluations Following Initial Diagnosis in Individuals with *GARS1*-Associated Axonal Neuropathy: Infantile-Onset Spinal Muscular Atrophy (*GARS1*-iSMA)

System/Concern	Evaluation	Comment
Constitutional	Assessment of growth parameters	Plotted on a standard growth chart
Gastrointestinal/ Feeding	Assessment for feeding dysfunction, gastroesophageal reflux disease, dysmotility incl constipation	• Incl eval of aspiration risk w/formal swallow study, nutritional status, & time required to complete a feed. • Consider eval for gastric tube placement in those w/ dysphagia &/or aspiration risk.
Respiratory	Assess pulmonary & respiratory function.	Refer to pulmonologist; consider a polysomnogram.
Musculoskeletal	Orthopedic, physical medicine & rehab, PT/OT eval	• Incl assessment of gross motor & fine motor skills. • Assess equipment needed for safety (car seat / car bed) & independence, such as power chair & other equipment in the home to improve quality of life for patient & caregiver.
Genetic counseling	By genetics professionals [1]	To inform families re nature, MOI, & implications of *GARS1*-iSMA in order to facilitate medical & personal decision making
Family support & resources	Assess: • Use of community or online resources; • Need for social work involvement for caretaker support.	

OT = occupational therapy; PT = physical therapy
1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Table 5. Recommended Evaluations Following Initial Diagnosis in Individuals with *GARS1*-Associated Axonal Neuropathy: Adolescent-/Adult-Onset Hereditary Motor/Sensory Neuropathy

System/Concern	Evaluation	Comment
Neurologic	Neurologic eval	• To determine extent of weakness & atrophy, *pes cavus*, gait stability, & sensory loss • To evaluate for pain • To evaluate for less common fixed manifestations (e.g., spasticity, hyperreflexia, ataxia)
Musculoskeletal/ ADL	Orthopedics, physical medicine & rehab, PT/OT eval	To incl assessment of: • Gross motor & fine motor skills & need for PT (to improve gross motor skills) &/or OT (to improve fine motor skills) • Feet for evidence of *pes cavus*, need for AFOs, specialized shoes • Mobility, ADL, & need for adaptive devices • Need for handicapped parking
Genetic counseling	By genetics professionals [1]	To inform patients & their families re nature, MOI, & implications of *GARS1*-HMSN in order to facilitate medical & personal decision making
Family support & resources	Assess: • Use of community or online resources; • Need for social work involvement for caretaker support.	

ADL = activities of daily living; MOI = mode of inheritance; OT = occupational therapist/therapy; PT = physical therapist/therapy
1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

GARS1 Infantile-Onset Spinal Muscular Atrophy (*GARS1*-iSMA)

Supportive treatment of children with *GARS1*-iSMA should be individualized to the needs of the affected individual and his/her current functional status (non-sitter, sitter, or walker). A multidisciplinary team to include a neurologist, pulmonologist, physiatrist, and medical geneticist is recommended.

Table 6. Supportive Treatment of Manifestations in Individuals with *GARS1*-Associated Axonal Neuropathy: Infantile-Onset Spinal Muscular Atrophy

Manifestation/ Concern	Specialty Referral	Treatment
Bulbar dysfunction	Gastroenterologist, licensed dietician, speech therapist, OT	• Clinical feeding eval & radiographic swallowing study • Nutritional supplementation • Placement of gastrostomy tube for aspiration concerns
Respiratory insufficiency	Pulmonologist, ENT, respiratory therapist, palliative care	• Noninvasive ventilation as indicated by pulmonary function testing, blood gas, & sleep study • Airway clearance techniques to incl cough assist devices & secretion mgmt • For patients w/severe respiratory involvement, discussions surrounding goals of immediate care vs long-term care & prognosis are imperative.
Neurogenic musculoskeletal abnormalities (e.g., scoliosis, hip dislocation, contractures)	Eval by PM&R, orthopedist, & PT/OT	• Bracing w/orthotics; range of motion exercises • Assistive devices to incl adaptive strollers, car seats, & wheelchairs • Surgical intervention for scoliosis & hip dislocation based on age, assoc pain, & functional benefit
Family/ Community	Palliative care, specialty nursing, & social work	• Ongoing assessment of need for palliative care involvement &/or home nursing • Ensure appropriate social work involvement to connect families w/local resources, respite, & support. • Assistance w/coordinating multiple subspecialty appointments

OT = occupational therapist; PM&R = physical medicine and rehabilitation; PT = physical therapist

GARS1 Adolescent- or Early Adult-Onset Hereditary Motor/Sensory Neuropathy (*GARS1*-HMSN)

Treatment is symptomatic. Affected individuals are often managed by a multidisciplinary team that includes neurologists, physiatrists, orthopedic surgeons, and physical and occupational therapists.

All individuals require assessment of their mobility needs and type of adaptations and devices that can be implemented to enhance their mobility. Devices include orthotics, which are often needed to correct foot drop and aid in walking.

Daily heel cord stretching helps prevent Achilles tendon shortening, foot deformities, and contractures.

Orthopedic surgery may be required for ankle fusion or to correct severe *pes cavus* deformity.

Some individuals require devices to assist with stability and mobility.

Numerous devices are available to facilitate various activities of daily living.

Surveillance

Table 7. Recommended Surveillance for Individuals with *GARS1*-Associated Axonal Neuropathy: Infantile-Onset Spinal Muscular Atrophy

System/Concern	Evaluation	Frequency
Growth	Plot growth parameters on standard growth chart.	At each visit or more often depending on severity of disease &/or need for additional intervention
Gastrointestinal/ Feeding	Oral feeders: aspiration risk, nutritional status, time to complete a feed	
	Gastric tube: nutritional status; constipation	
Respiratory	Non-ventilator dependent: work on breathing, oxygenation, & ability to manage secretions.	
	Ventilator dependent: ventilation, oxygenation, & secretions	
Musculoskeletal	OT, PT assessment of gross motor skills, mobility, need for assistive devices, activities of daily living	
	Orthopedist eval for kyphoscoliosis, contractures, hip dislocation	
Development	Monitor developmental progress & educational needs.	
Family support & resources	Assess family need for social work support (e.g., palliative/respite care, home nursing, other local resources) & care coordination.	

OT = occupational therapist; PT = physical therapist

Table 8. Recommended Surveillance for Individuals with *GARS1*-Associated Axonal Neuropathy: Adolescent-/Adult-Onset Hereditary Motor/Sensory Neuropathy

System/Concern	Evaluation	Frequency
Neurologic	• Screening neurologic exam w/focus on progression of limb weakness • Eval for pain	Annually or more often depending on disease progression & patient needs
Musculoskeletal, activities of daily living & mobility	• PT • OT • PM&R assessment for adaptive & mobility devices • Primary care/neurologist/patient: comprehensive dermatologic assessment to assess for pressure ulcers or sores & skin breakdown; particular attention to feet, hips, & other pressure points	

OT = occupational therapist; PM&R = physical medicine and rehabilitation; PT = physical therapist

Agents/Circumstances to Avoid

Medications that are toxic or potentially toxic to persons with HMSN comprise a spectrum of risk ranging from definite high risk to negligible risk. See the Charcot-Marie-Tooth Association website (pdf) for an up-to-date list.

Chemotherapy for cancer that includes vincristine may be especially damaging to peripheral nerves and may severely worsen HMSN [Nishikawa et al 2008].

Given the relatively few individuals reported with *GARS1*-iSMA and limited longitudinal follow up, avoidance of neurotoxic (and potentially neurotoxic) medications would be appropriate despite the current lack of data.

Evaluation of Relatives at Risk

It is appropriate to clarify the genetic status of apparently asymptomatic older and younger at-risk relatives of an individual with *GARS1*-HMSN in order to identify as early as possible those who would benefit from prompt initiation of treatment and awareness of agents and circumstances to avoid.

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Therapies Under Investigation

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

GARS1 infantile-onset spinal muscular atrophy is an autosomal dominant disorder; in all individuals reported to date, it has been caused by a *de novo* pathogenic variant.

GARS1 adolescent- or early adult-onset hereditary motor/sensory neuropathy (encompassing the phenotypes also referred to as Charcot-Marie-Tooth neuropathy type 2D and distal spinal muscular atrophy V) is an autosomal dominant disorder caused by an inherited or *de novo* pathogenic variant.

Risk to Family Members

GARS1 Infantile-Onset Spinal Muscular Atrophy (*GARS1*-iSMA)

Parents of a proband

- All probands reported to date with *GARS1*-iSMA whose parents have undergone molecular genetic testing have the disorder as a result of a *de novo GARS1* pathogenic variant.
- Molecular genetic testing is recommended for the parents of the proband to confirm their genetic status and to allow reliable recurrence risk counseling.
- If the pathogenic variant identified in the proband is not identified in either parent, the following possibilities should be considered:
  - The proband has a *de novo* pathogenic variant. Note: A pathogenic variant is reported as "*de novo*" if: (1) the pathogenic variant found in the proband is not detected in parental DNA; and (2) parental identity testing has confirmed biological maternity and paternity. If parental identity testing is not performed, the variant is reported as "assumed *de novo*" [Richards et al 2015].
  - The proband inherited a pathogenic variant from a parent with germline (or somatic and germline) mosaicism. Note: Testing of parental leukocyte DNA may not detect all instances of somatic mosaicism and will not detect a pathogenic variant that is present in the germ cells only.

Sibs of a proband. The risk to sibs of the proband depends on the genetic status of the proband's parents:

- If a parent of the proband is known to have the *GARS1* pathogenic variant identified in the proband, the risk to the sibs of inheriting the pathogenic variant is 50%.
- If the *GARS1* pathogenic variant cannot be detected in the leukocyte DNA of either parent, the recurrence risk to sibs is estimated to be 1% because of the theoretic possibility of parental germline mosaicism [Rahbari et al 2016].

Offspring of a proband. Individuals with *GARS1*-iSMA are not known to reproduce; however, many are not yet of reproductive age.

Other family members. Given that all probands with *GARS1*-iSMA reported to date have the disorder as a result of a *de novo GARS1* pathogenic variant, the risk to other family members is presumed to be low.

GARS1 Adolescent- or Early Adult-Onset Hereditary Motor/Sensory Neuropathy (*GARS1*-HMSN)

Parents of a proband

- Most individuals diagnosed with *GARS1*-HMSN have an affected parent.
- A proband with *GARS1*-HMSN may have the disorder as the result of a *de novo* pathogenic variant; the proportion of individuals with *GARS1*-HMSN caused by a *de novo* pathogenic variant is unknown.
- Molecular genetic testing is recommended for the parents of the proband to confirm their genetic status and to allow reliable recurrence risk counseling.
- If the pathogenic variant identified in the proband is not identified in either parent, the following possibilities should be considered:
  - The proband has a *de novo* pathogenic variant. Note: A pathogenic variant is reported as "*de novo*" if: (1) the pathogenic variant found in the proband is not detected in parental DNA; and (2) parental identity testing has confirmed biological maternity and paternity. If parental identity testing is not performed, the variant is reported as "assumed *de novo*" [Richards et al 2015].
  - The proband inherited a pathogenic variant from a parent with germline (or somatic and germline) mosaicism. Note: Testing of parental leukocyte DNA may not detect all instances of somatic mosaicism and will not detect a pathogenic variant that is present in the germ cells only.
- The family history of some individuals diagnosed with *GARS1*-HMSN may appear to be negative because of failure by health care professionals to recognize the syndrome, a milder phenotypic presentation, early death of a parent before the onset of symptoms, and/or late onset of the disorder. Therefore, an apparently negative family history cannot be confirmed unless molecular genetic testing has demonstrated that neither parent is heterozygous for the pathogenic variant identified in the proband.

Sibs of a proband. The risk to sibs of the proband depends on the clinical/genetic status of the proband's parents:

- If a parent of the proband is affected and/or is known to have the pathogenic variant identified in the proband, the risk to the sibs of inheriting the pathogenic variant is 50%.
- Intrafamilial clinical variability and reduced penetrance have been observed in *GARS1*-HMSN.
- If the *GARS1* pathogenic variant cannot be detected in the leukocyte DNA of either parent, the recurrence risk to sibs is estimated to be 1% because of the theoretic possibility of parental germline mosaicism [Rahbari et al 2016].
- If the parents have not been tested for the *GARS1* pathogenic variant but are clinically unaffected, the risk to the sibs of a proband appears to be low. However, sibs of a proband with clinically unaffected parents are still presumed to be at increased risk for *GARS1*-HMSN because of the possibility of reduced penetrance in a parent or the theoretic possibility of parental germline mosaicism.

Offspring of a proband. Each child of an individual with *GARS1*-HMSN is at a 50% risk of inheriting the *GARS1* pathogenic variant.

Other family members. The risk to other family members depends on the genetic status of the proband's parents; if a parent is affected and/or has the *GARS1* pathogenic variant, his or her family members are at risk.

Related Genetic Counseling Issues

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected or at risk.

Prenatal Testing and Preimplantation Genetic Testing

Once the *GARS1* pathogenic variant has been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **Charcot-Marie-Tooth Association (CMTA)**
  Phone: 800-606-2682
  Email: info@cmtausa.org
  cmtausa.org
- **European Charcot-Marie-Tooth Consortium**
  Department of Molecular Genetics
  University of Antwerp
  Antwerp Antwerpen B-2610
  Belgium
  Fax: 03 2651002
  Email: gisele.smeyers@ua.ac.be
- **Hereditary Neuropathy Foundation**
  Phone: 855-435-7268 (toll-free); 212-722-8396
  Fax: 917-591-2758
  Email: info@hnf-cure.org
  www.hnf-cure.org
- **Muscular Dystrophy Association (MDA) - USA**
  Phone: 833-275-6321
  Email: ResourceCenter@mdausa.org
  mda.org

- **RDCRN Patient Contact Registry: Inherited Neuropathies Consortium**
  Patient Contact Registry

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. GARS-Associated Axonal Neuropathy: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
GARS1	7p14.3	Glycine--tRNA ligase	alsod/GARS genetic mutations GARS homepage - Leiden Muscular Dystrophy pages	GARS1	GARS1

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for GARS-Associated Axonal Neuropathy (View All in OMIM)

600287	GLYCYL-tRNA SYNTHETASE 1; GARS1
600794	NEURONOPATHY, DISTAL HEREDITARY MOTOR, AUTOSOMAL DOMINANT 5; HMND5
601472	CHARCOT-MARIE-TOOTH DISEASE, AXONAL, TYPE 2D; CMT2D
619042	SPINAL MUSCULAR ATROPHY, INFANTILE, JAMES TYPE; SMAJI

Molecular Pathogenesis

The molecular pathology that underlies the spectrum of neuromuscular and sensory phenotypes observed in *GARS1*-associated axonal neuropathy is unclear.

The protein GARS, which functions as a homodimer, is a member of the ubiquitously expressed aminoacyl-tRNA synthetase family whose key function is charging tRNA with glycine. GARS comprises an N-terminal appended WHEP-TRS domain, a catalytic core, and a C-terminal anticodon binding domain. Variants in *GARS* that encode each of these domains lead to axonal neuropathy [Antonellis et al 2003, Griffin et al 2014]. Functional studies in mice [Seburn et al 2014], yeast [Griffin et al 2014], zebrafish [Malissovas et al 2016], and in vitro [Griffin et al 2014] have confirmed the importance of the GARS catalytic, anti-codon binding, and dimerization domains in disease.

While absence of phenotypes in heterozygous null variants in mice provides evidence against haploinsufficiency [Seburn et al 2014], several variants resulting in impaired dimerization, anti-codon binding, or catalytic activity of GARS have been shown to contribute to the molecular and phenotypic overlap of the two HMSN subtypes, Charcot-Marie-Tooth neuropathy type 2D (CMT2D) and distal spinal muscular atrophy V (dSMA-V) [Griffin et al 2014, Malissovas et al 2016].

An overview of the gene-disease association can be found here.

Mechanism of disease causation. Not established

Table 9. Notable *GARS1* Pathogenic Variants

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change (Alias [1])	Associated Phenotype [Reference]
NM_002047.4 NP_002038.2	c.332C>T	p.Ala111Val (p.Ala57Val)	*GARS1*-HMSN (CMT2D). Likely hypomorphic variant [Griffin et al 2014]
	c.374A>G	p.Glu125Gly (p.Glu71Gly)	*GARS1*-HMSN (CMT2D & dSMA-V) [Antonellis et al 2003, He et al 2015]
	c.548T>C	p.Leu183Pro (p.Leu129Pro)	*GARS1*-HMSN (exclusively dSMA-V) [Antonellis et al 2003, He et al 2015]
	c.598G>T	p.Asp200Tyr (p.Asp146Tyr)	*GARS1*-HMSN (early-onset axonal CMT) [Liao et al 2015]
	c.880G>C	p.Gly294Arg (p.Gly240Arg)	*GARS1*-HMSN (CMT2D) [Antonellis et al 2003, He et al 2015, Malissovas et al 2016]
	c.893C>T	p.Pro298Leu (p.Pro244Leu)	*GARS1*-HMSN (CMT2D & dSMA-V) [Abe & Hayasaka 2009, Griffin et al 2014]
	c.1000A>T	p.Ile334Phe (p.Ile280Phe)	*GARS1*-HMSN (CMT2D) [James et al 2006, Griffin et al 2014]
	c.1001T>A	p.Ile334Asn (p.Ile280Asn)	*GARS1*-iSMA [Markovitz et al 2020]
	c.1415A>G	p.His472Arg (p.His418Arg)	*GARS1*-HMSN (exclusively dSMA-V) [Sivakumar et al 2005, Griffin et al 2014, Cortese et al 2020, Lin et al 2020]
	c.1954G>C	p.Gly652Arg	*GARS1*-iSMA [Markovitz et al 2020]
	c.1955G>C	p.Gly652Ala (p.Gly598Ala)	*GARS1*-iSMA [James et al 2006, Eskuri et al 2012]
	c.1660G>A	p.Asp554Asn (p.Asp500Asn)	*GARS1*-HMSN (CMT2D & dSMA-V) [Del Bo et al 2006]
	c.1738G>C	p.Gly580Arg (p.Gly526Arg)	*GARS1*-HMSN (CMT2D) [Antonellis et al 2003, Dubourg et al 2006]

CMT2D = Charcot-Marie-Tooth neuropathy type 2D (distal motor and sensory involvement); dSMA-V = distal spinal muscular atrophy V (distal motor involvement exclusively)

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.

GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.

1. There are two isoforms of *GARS1* (www.uniprot.org/uniprot/P41250#sequences). In the literature both isoforms are used. The longest transcript is used as the reference sequence. Isoform 2 is shorter, and does not include amino acids 1-54.

Chapter Notes

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- 22 July 2021 (bp) Comprehensive update posted live
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- 25 August 2011 (me) Comprehensive update posted live
- 30 January 2007 (lgg) Revision: sequence analysis clinically available for mutations in *GARS*
- 8 November 2006 (me) Review posted live
- 24 February 2006 (lgg) Original submission

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